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# Preimplantation genetic testing significantly improves in vitro fertilization outcome in all patient age groups: An analysis of 181,609 cycles from SART National Summary Report

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## Abstract

**Purpose:** To study whether preimplantation genetic testing (PGT) improves embryo implantation and live birth in patients undergoing in vitro fertilization (IVF).

**Materials and methods:** The SART National Summary Reports from 2014 to 2019 were used for this study. Cycle inclusion criteria were day 5/6 elective single embryo transfers (eSET), fresh embryo transfers (ET), the first frozen embryo transfers without PGT (FET) or with PGT (FET/PGT). Exclusion criteria were use of gestational carriers and donor eggs/embryos. Clinical outcomes included embryo implantation, live birth, and miscarriage rates. $X^2$ tests were used for statistical analysis.

**Results:** A total of 181,609 eSETs were analyzed for the effect of PGT on IVF outcomes including 65,419 ET, 33,175 first FET and 83,015 first FET/PGT cycles. Rates of both live birth and implantation were significantly higher in patients with FET/PGT than those in the ET and FET groups in both < 35 and ≥ 35 age groups ($P < 0.0001$). Miscarriage rates with FET were significantly higher in both age groups than those with ET. Miscarriage rates with FET/PGT were significantly lower than those with ET or FET in both age groups.

**Conclusion:** This study using large cohort SART data demonstrates that PGT significantly improves IVF outcome in all patient age groups. We also found that patients in the first FET attempt had significant higher embryo implantation and live birth compared to fresh ET.

## Introduction

The first PGT was reported in 1990 [1] as an alternative to prenatal genetic testing for monogenic disorders. In the latter 1990s this technology was increasingly used for detection of chromosomal structural abnormalities or for aneuploidy screening (PGT-A) with fluorescence in situ hybridization (FISH).

Aneuploid is very common in human preimplantation embryos and is the main cause of embryo implantation failure and miscarriage. From the latter 1990s to the first decade of this century, Day 3 embryo biopsy was gradually adopted for PGT-A with FISH. Conflicting reports existed about its effectiveness when used in patients with repeat miscarriage, IVF failure, or advanced age [2-8]. A small randomized clinical trial did not show improvement of IVF outcomes for unexplained recurrent miscarriages [2]. The European Society of Human Reproduction and Embryology PGT Consortium data did not show any improvement in clinical IVF outcomes for patients with repeat IVF failures [3]. In a large randomized clinical trial, Mastenbroek and his colleagues found that PGT-A with day 3 biopsy significantly reduced, rather than increased, the likelihood of an ongoing pregnancy or live birth in women with advance maternal age [8]. Several reasons may be responsible for the failure of PGT-A to improve IVF outcome. The first is misdiagnosis, including false positive or false negative results due to mosaicism or technical issues; secondly, limited chromosomes can be detected with FISH method; and third, day 3 embryo biopsy may compromise embryo implantation potential [9].

At the beginning of the last decade, trophectoderm biopsy gained use to facilitate PGT-A. With the advance of new technologies including better embryo culture methods, vitrification instead of slow-freezing, and PCR based genotyping to detect all 23 pairs of chromosomes, trophectoderm biopsy for PGT-A has become one of the most important tools in IVF treatment. Several randomized clinical trials (RCTs) demonstrated that both implantation and delivery rates were significantly higher after PGT-A than without genetic testing [10-12]. Today, trophectoderm biopsy for PGT-A has been widely adopted by IVF programs throughout the world. In the US, the fresh embryo transfers without PGT-A have gradually decreased, and frozen embryo transfers with PGT-A have more than doubled from 2014 to 2017 [13].

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**Table 1.** Clinical outcomes in patients undergoing IVF treatment at the first attempt with elective single fresh embryo transfer, frozen embryo transfer or frozen embryo transfer post PGT

| Outcome | < 35 | | | ≥ 35 | | |
|---|---|---|---|---|---|---|
| | ET | FET | FET/PGT | ET | FET | FET/PGT |
| **# of transfers** | 46,863 | 24,014 | 37,090 | 18,556 | 9,161 | 45,925 |
| **Clinical pregnancy (%)** | 57.0 | 62.6 | 66.4 | 47.2 | 53.1 | 65.3 |
| **Miscarriage (%)** | 11.9 | 15.3 | 11.1 | 19.0 | 21.8 | 12.7 |
| **Implantation (%)** | 55.6 | 59.5 | 63.9 | 44.7 | 49.1 | 62.4 |
| **Live Birth (%)** | 49.2 | 52.1 | 58.1 | 37.1 | 40.4 | 56.1 |
| ***P* values** | PGT vs ET | PGT vs FET | FET vs ET | PGT vs ET | PGT vs FET | FET vs ET |
| **Clinical pregnancy (%)** | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Miscarriage (%)** | 0.004 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.001 |
| **Implantation (%)** | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| **Live Birth (%)** | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |

Though PGT-A is essentially universally offered or available to all IVF patients, the benefit vs. risk is still not a settled issue. In 2019, Munne and his colleagues published a multicenter RCT [14]. In that study, they found that PGT-A showed no overall improvement in on-going pregnancy/live birth in patients aged 25-40, but does support the use of PGT-A for patients age 35-40. The results were unexpected and contrary to findings of many previous randomized studies [10-12]. RCTs are often considered the gold standard in clinical research, but the limitation is that the number of enrollments is almost always very limited. SART collects IVF data from the majority of IVF programs in the US, representing almost the entire population of IVF cycles performed in the US. Hence, in this study, utilizing the high volumes of data available through SART, we explored a different way to answer the same question of whether PGT improves IVF outcome in terms of embryo implantation, live birth, and miscarriage rate by analyzing data which we believe represent the majority population of autologous IVF cycles in the US.

## Materials and methods

In the United States, the majority of IVF programs report IVF outcomes to SART, which are then published annually on the SART.org website as the National Summary Report. We used the National Summary Report data from 2014 to 2019 for this study. Inclusion criteria were elective single embryo transfer (eSET), fresh embryo transfer (ET), frozen embryo transfer (FET), and frozen embryo transfer post PGT (FET/PGT). Exclusion criteria were use of gestational carriers, donor eggs, or donated embryos. The cohort flow diagram of the study is illustrated in Figure 1. In total, 1,459,721 cycles were reported from 2014 to 2019. After exclusion of gestational carriers and transfers with multiple embryos, 361,103 transfers were by eSET on day 5/6. After exclusion of donor eggs and donated embryos, total of 308,973 transfers were by eSET with autologous eggs and were included in the study for final analyses. Among them, 65,419 cycles were by fresh ET, 33,175 were the first FET per intended egg retrieval, and 83,015 were the first FET/PGT per intended egg retrieval. Key IVF outcomes include live births, embryo implantation, and miscarriage rates stratified into age groups <35, 35-37, 38-40, >40 years among patients with or without PGT. The main outcomes were described as percentages. Chi-squared test was used for statistical analyses between categorical variables. Two-tailed P values of <0.05 were considered statistically significant.

## Results

To evaluate whether PGT truly improves reproductive outcome in terms of live birth rate, pregnancy rate, implantation rate and spontaneous miscarriage rate, this retrospective cohort study aimed to capture all autologous IVF cycles with an elective single embryo transfer reported to SART. Between 2014 and 2019, a total of 361,103 IVF cycles were eSET with autologous eggs. Excluding those subsequent FET cycles with or without PGT, a total of 181,609 eSET were included for the final analysis. Among the cycles, 65,419 cycles were fresh ET, 33,175 cycles were the first FET and 83,015 cycles were the first FET post PGT after the initial egg retrieval (Figure 1 and Table 1).

Live birth rate was 58.1% in the patients < 35 in the FET/PGT group, which was significantly higher than those in the ET and FET groups (49.2% and 52.1%, P < 0.0001, Figure 1 and Table 1). Live birth rate in patients in the 35-37 age group in the FET/PGT were 57.1%, significantly higher than 41.1% in the ET and 44.5% in the FET (P < 0.0001, Figure 1A). In the 38-40 patient age group, live birth was 55.6% in the FET/PGT, compared with 30.2% and 35.8% in the ET and FET (P < 0.0001, Figure 1). The difference of live birth rates among the FET/PGT, ET and FET in patients > 40 were further increased (53.1% vs 12.1% and 23.4%, P < 0.0001, Figure 1A). Live birth rates in all patient age groups after FET were all significantly higher than those in the ET group (P < 0.0001, Figure 2 and Table 2).

Embryo implantation rate was 63.9% in the patients < 35 in the FET/PGT group (Figure 1 and Table 1), significantly higher than 55.6% in the ET (P < 0.0001) and 59.5% in the FET (P < 0.0001). Among other age subgroups, findings were similar. Implantation rate in the FET/PGT were 63.2% vs 48.4% and 52.8% in the 35-37 age group (P < 0.0001, Figure 1B), 62.1% and 59.7% respectively in the 38-40 and >40 age groups after FET/PGT, vs 38.8% and 18.5% after ET (P < 0.0001), as well as 44.9% and 33.4% after FET (P < 0.0001). Implantation rates in all age groups after FETs were significantly higher than those after ETs (P < 0.0001, Figure 2 and Table 2).

Miscarriage rates were very similar among groups of patients < 35, but due to the nature of large sample size, miscarriage rate after FET/PGT was statistically significantly lower than those in ET and FET groups (FET/PGT vs ET, P = 0.004 and FET/PGT vs FET, P < 0.0001, Figure 1 and Table 1). In all other age groups, miscarriage rates after FET/PGT were significantly lower than those after ET or FET (P < 0.0001, Figure 2 and Table 1). Miscarriage rates after FET were significantly higher than those after ET in both <35 and 35-37 age groups (15.3% vs 11.9%, P < 0.0001 and 19.7% vs 17.0%, p<0.001, Figure 2C), while there were no statistical differences in the 38-40 (24.0% vs 24.7%, P > 0.05) and >40 age groups (37.2% vs 38.4%, p>0.05).

## Discussion

Using the National Summary Report data from 2014 to 2019, we found that FET/PGT not only significantly increased embryo implantation and live birth, but also significantly decreased miscarriage rates in all age groups of patients undergoing IVF treatment. Our data

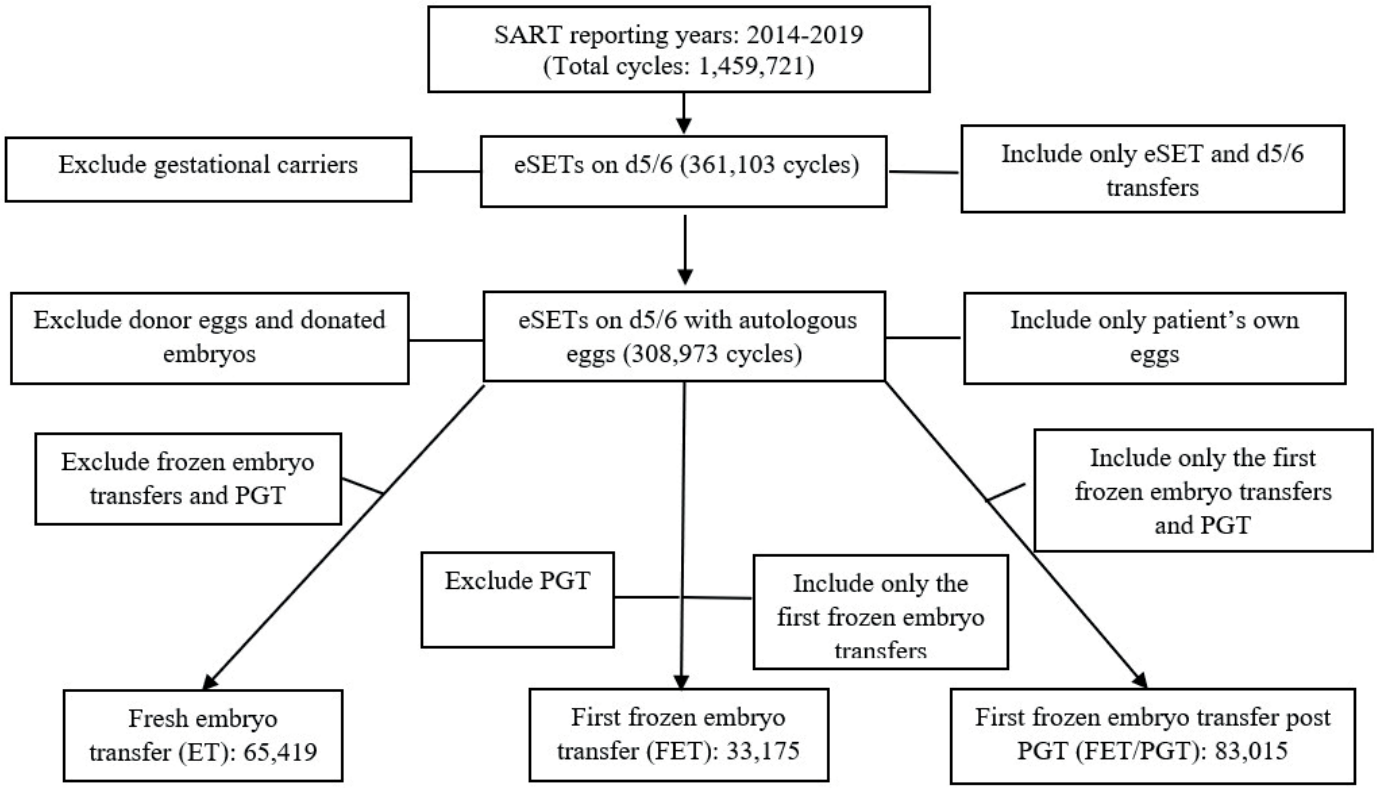



**Figure 1.** Study design flow diagram

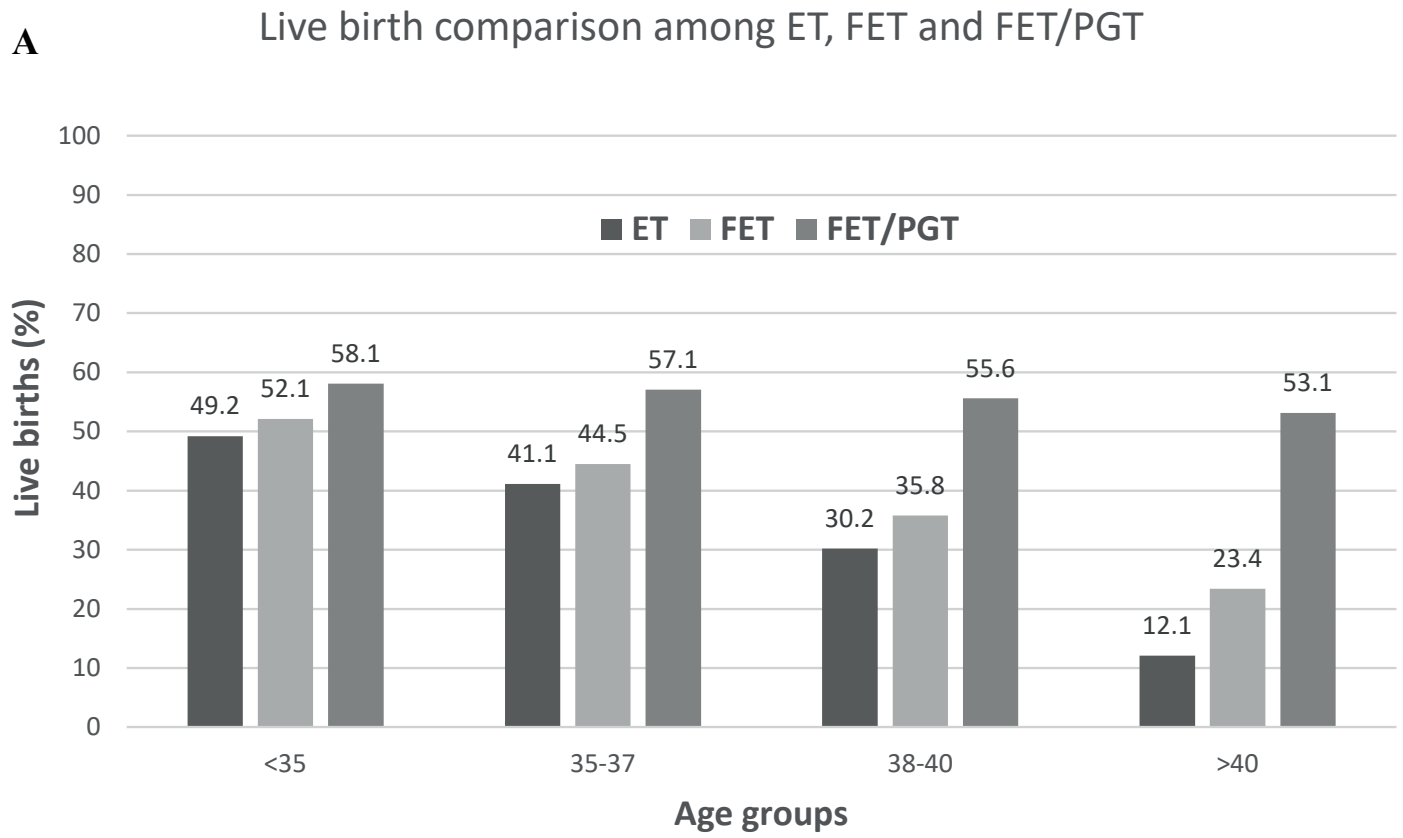
also demonstrates that FET in the first attempt following the initial IVF cycle without PGT also increased implantation and live birth when compared with fresh ET.

Aneuploidy is a very common finding in human embryos derived from IVF and are less likely to implant. Even if they do, chances of early pregnancy loss are very high. Aneuploidy rates naturally increase as individuals age, often manifesting earlier in women compared to men. About 80% of embryos are aneuploid with women over 40 years old [15]. PGT-A provides patients with an opportunity to improve reproductive outcomes in women attempting conception and reduce the risk of delivering a child with a genetic abnormality through identification of a euploid embryo for transfer. PGT-A has been used in IVF since the first PGT report 30 years ago [1]. FISH method to identify euploid embryos with day 3 embryo or polar body biopsies was not ideal in the early years of PGT-A [7,8]. A large RCT demonstrated that PGT-A significantly reduced rather than increased embryo implantation and live births in women of advanced age undergoing IVF [8]. Several reasons could explain the failure of PGT-A to improve IVF outcome. The limitation in the number of chromosomes which could be tested with FISH may have resulted in transferring embryos which were diploid for those chromosomes tested but possessed aneuploidy on an untested chromosome. One blastomere biopsied from cleavage stage embryos for PGT-A may not be representative of the whole embryo due to high percentage of mosaicism in human embryos from IVF, which could lead to transfer of aneuploid embryos or embryos with high mosaicism. Furthermore, cleavage-stage embryo biopsy significantly reduces embryonic reproductive potential [9].

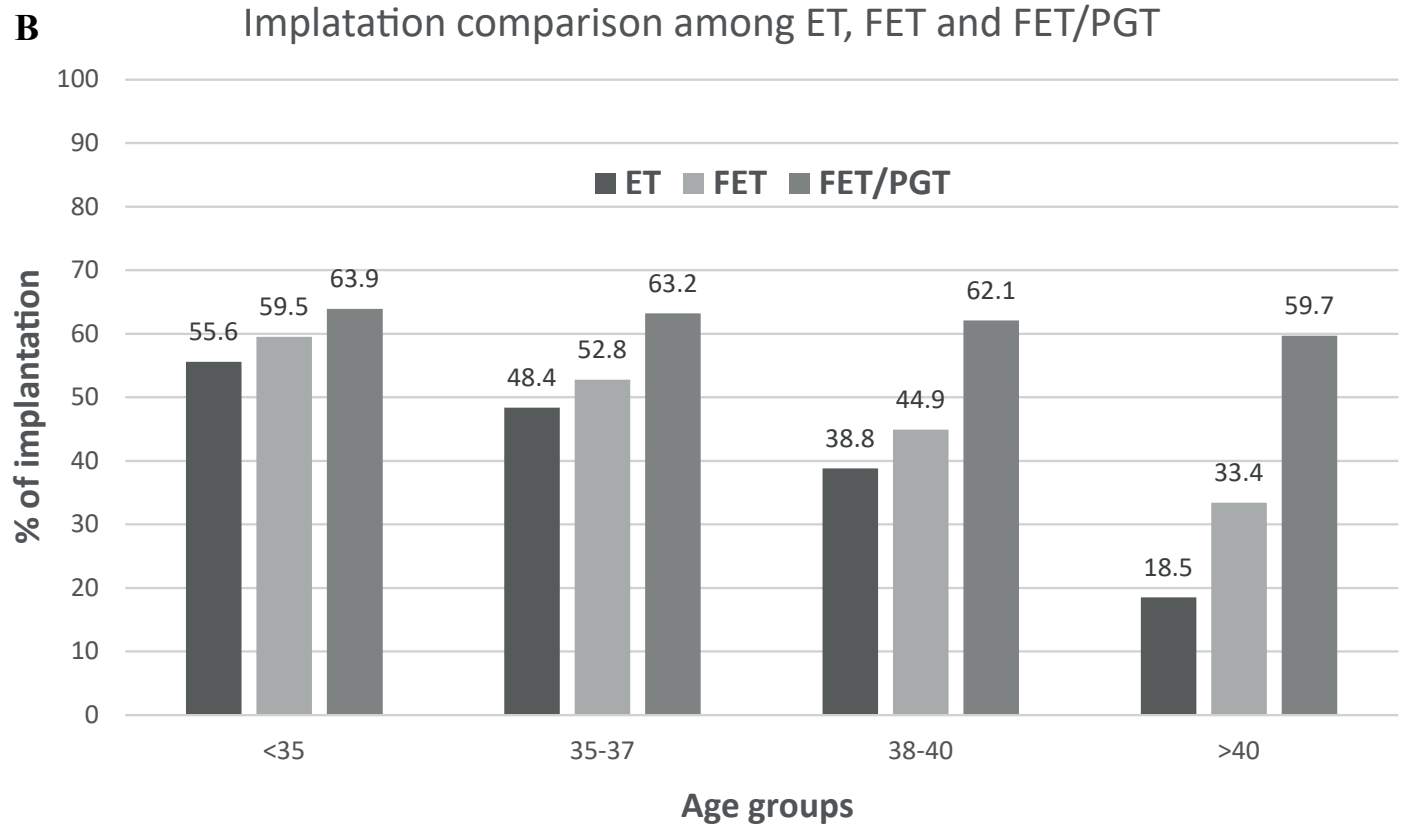
Trophectoderm biopsy and PCR based 24-chromosome screening provide new opportunities in improving fertility outcomes [10-12]. Comparative genomic hybridization array, single nucleotide polymorphism array and next generation sequencing are widely used for PGT-A [15]. Nowadays, almost all PGT-A is performed with trophectoderm biopsy for all 24-chromosome screening. In a randomized pilot study, Yang and his colleagues found that PGT-A with trophectoderm biopsy significantly increased pregnancy and on-going pregnancies in relatively young and good prognosis IVF patients [10]. Scott and his colleagues provided further evidence that PGT-A using qPCR with 24-chromosome screening significantly improved embryo implantation and live birth rates [12]. In patients with advanced maternal age, Rubio et al demonstrated the superiority of PGT-A in achieving live birth at the first attempt both per transfer and per cycle [11]. They also found significantly lower miscarriage rates in patients after PGT-A. However, in a recent multicenter RCT, Munne et al. found that PGT-A did not improve overall pregnancy outcomes in all women per intention to treat. In patients younger than age 35, PGT-A actually decreased ongoing pregnancies per embryo transfer [14]. These results were unexpected and opposite to findings of many previous randomized studies [10-12], though there were many limitations to the study. First was lack of standardization between the enrollment centers for the study. Secondly, the variation of euploid rate between the top enrolling centers were huge, from 38% to 100% in younger patients and 17% to 75% in older patients. Third, the variation in ongoing pregnancy or live births at different centers ranged from 30% to 60%.

Though RCTs are considered the gold standard for clinical studies, the major downside is that the number of patients recruited for such studies is always very limited. In reproductive medicine, the factors that influence IVF outcome are not just patients themselves, but include many other known and unknown variables, such as stimulation management, egg retrieval efficiency, embryo transfer technique, IVF laboratory conditions, variation in trophectoderm biopsy technique, and embryo freezing and thawing techniques, all of which can have

**A**


Live birth comparison among ET, FET and FET/PGT
ET
FET
FET/PGT
Live births (%)
100
90
80
70
60
50
40
30
20
10
0
49.2
52.1
58.1
41.1
44.5
57.1
30.2
35.8
55.6
12.1
23.4
53.1
<35
35-37
38-40
>40
Age groups

**B**


Implatation comparison among ET, FET and FET/PGT
ET
FET
FET/PGT
% of implantation
100
90
80
70
60
50
40
30
20
10
0
55.6
59.5
63.9
48.4
52.8
63.2
38.8
44.9
62.1
18.5
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<35
35-37
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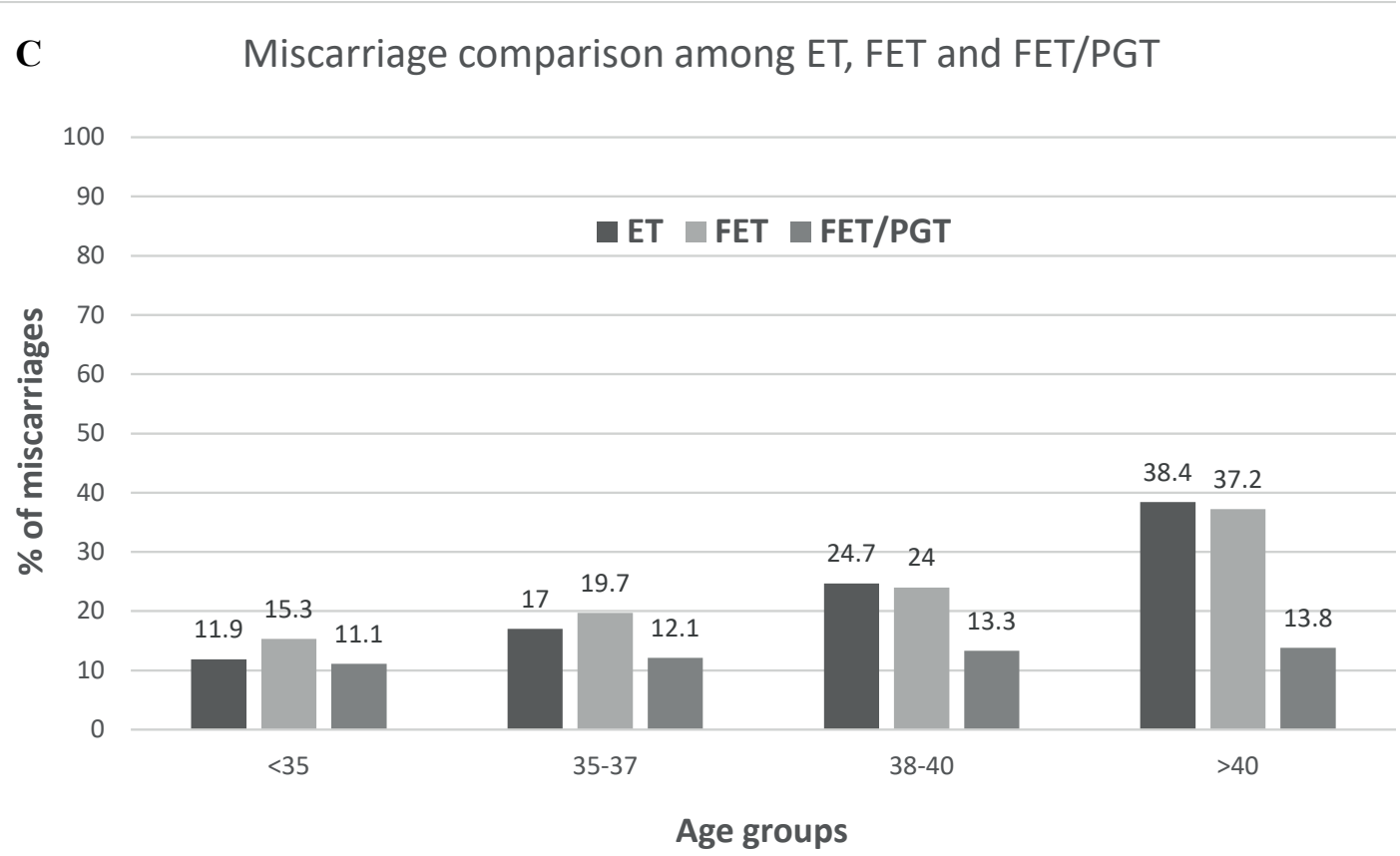
>40
Age groups




| | Number of transfers | | | |
|---|---|---|---|---|
| | <35 | 35-37 | 38-40 | >40 |
| **ET** | 46,863 | 13630 | 3873 | 1053 |
| **FET** | 24,014 | 6014 | 2347 | 800 |
| **FET/PGT** | 37,090 | 23243 | 17196 | 5486 |

**Figure 2.** Comparison of live birth, implantation and miscarriage rates among ET, FET, and FET/PGT in different age groups. The number of transfers in each treatment groups was included in the table.

a. Live birth rates:
FET/PGT vs ET and FET, $P < 0.0001$ in all age groups
FET vs ET, $P < 0.0001$ in all age groups

b. Implantation rates:
FET/PGT vs ET and FET, $P < 0.0001$ in all age groups
FET vs ET, $P < 0.0001$ in all age groups

c. Miscarriage rates:
FET/PGT vs ET and FET, $P = 0.004$ and $< 0.0001$, respectively in the age group of < 35; $P < 0.0001$ in all other groups
FET vs ET, $P < 0.0001$ in the age < 35 and $P < 0.001$ in the age 35-37 groups; there was no statistical difference among the other age groups ($P > 0.05$)

potentially significant effects on IVF outcome. In RCTs, it is impractical to adequately control all these variables, even with a large sample size. To find out the effectiveness of PGT-A in improving IVF outcome, an ideal approach would not take samples from an IVF population, but rather utilize the population as a whole. The SART dataset provides the closest approximation to such a population for IVF in the US, and would eliminate the majority of known or unknown patient, laboratory, and IVF program-specific variables. In this study, we collected 6 years of SART Annual National Summary Report data to address whether PGT is truly useful in improving IVF outcomes. With the largest dataset available in the US, we demonstrated that PGT significantly improved IVF outcome. Live birth was 49.1% in fresh ET without PGT in the age group < 35 years old, compared with 58.1% after PGT, which is an almost 9% increase compared with fresh ET and 6% increase compared with first FET (Figure 1A). In the patients > 40 years old, the difference of live birth rates widens to 41% (Figure 1). The same pattern was found in the embryo implantation (Figure 1). These findings further demonstrate that aneuploidy is the major cause of embryo implantation failure in IVF. There was marginal difference in miscarriage rates in the patients < 35 years old between fresh ET and FET/PGT, but the differences increased gradually from younger to older groups (Figure 1). When patients were older than 40, miscarriage rates decrease from 38.4% to 13.8% after PGT, suggesting that miscarriage is the other main cause of IVF failures, especially in older patients.

Freezing-all embryos in the initial cycle to prevent severe ovarian hyperstimulation syndrome (OHSS) has become common practice in many IVF programs. Studies have shown that FET, compared with fresh ET, significantly improves pregnancy and live birth rates [16,17]. Higher

perinatal morbidity in pregnancies conceived after a fresh ET than FET also favors FET in recent trends in IVF treatment [18]. On the other hand, some studies found that FET carries an increased risk of high birth weight and large for gestational age infants [19-21]. Additionally, preeclampsia has been shown to be more common in pregnancies from FET compared with both natural conception and pregnancies from fresh ET [22,23]. A recent study from SART dataset shows that both live birth and embryo implantation rates were significantly lower in FET compared with those in ET, and the miscarriage rate after FET was significantly higher than that after ET [13]. In that SART dataset study, clinical outcome in FET contains both the first and subsequent FETs, therefore it is possible that the best quality embryos were selected in ET, while in FET, embryo quality may be inferior in the subsequent FET cycles. In this study, we found that both embryo implantation and live birth rates with the first FET after the initial IVF cycle were significantly higher than those with ET in all age groups (Figure 2B). While miscarriage rates in FET are significantly higher than those in the ET (Figure 2C, Table 1), increased miscarriage may stem from a variety of reasons such as poor blastocyst quality in the FET group, or possibly due to embryo damage during the freezing/thawing process. Because only the first FET was included in this study, it is a greater likelihood that the increased miscarriage in the FET may not be related to embryo quality, but more likely from blastocyst damage during the freezing/thawing process. It is well established that slow-freezing leads to more damage to embryos compared to vitrification. Though more recently, the majority of IVF laboratories use the vitrification method, some blastocysts in the FET group, especially from earlier years, may have been frozen via the slow-freezing technique. Those blastocysts implant, but may be more likely to miscarry later on, and could partly explain higher miscarriage rates in the FET group. The SART data did not specify which freezing method was used for embryos in FET. Higher embryo implantation and live birth rates in the FET group compared to the ET group indicate that the overall benefits overcome the shortfalls of potential embryo damage from freezing/thawing process in terms of overall IVF outcome.

This retrospective cohort study has aimed to capture the majority PGTs since SART's National Summary Report started in 2014. To address whether PGT really improves IVF outcome, we only included the first FET/PGT or FET attempt with eSET for analysis. The main strength of the study is the use of large cohort data from 2014 to 2019, covering the majority of IVF programs in United States, to achieve the closest approximation to observation of the whole US IVF population during that time span. The large cycle numbers derived from national data significantly minimizes confounding factors such as the many known or unknown variables related to IVF success, which were encountered in many previous RCTs. The weakness of the study is that the data were collected from the SART National Summary Report, so we were not able to distinguish PGT-A from other PGTs such as PGT-M/PGT-SR, though the latter only accounts for a small proportion of total PGTs. The other weakness of the study is that some confounding factors which may affect IVF outcome, such as patient BMI or etiology of infertility, were not available. While there is a limitation that the data were extrapolated from the SART Annual Summary Report, the sheer cohort size used in our data analyses significantly minimizes the chance that any error encountered from the extrapolated data would have impacted our findings given their statistical significance.

In conclusion, PGT has developed into one of the most important aspects of IVF treatment. This study using large cohort SART data demonstrates that PGT significantly improves IVF outcome in all patient age groups. We also found that patients in the first FET attempt had significant higher embryo implantation and live births compared to fresh ET, suggesting the freezing all practice may not only reduce OHSS, but also improve IVF outcome. With a trend toward decreasing costs over time and broad availability, it is reasonable to consider adoption of PGT with FET as the standard of care in IVF treatment.

## Declarations

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Code availability: Not applicable

Ethics approval: Not applicable

Consent to participate: Not applicable

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